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ORIGINAL REPORT

Impact of Long-Term Serum Platinum Concentrations on Neuro- and Ototoxicity in Cisplatin-Treated Survivors of Testicular Cancer

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ABSTRACT

Purpose
Cisplatin-induced neurotoxicity and ototoxicity (NTX) are important adverse effects after chemotherapy for testicular cancer (TC). Although serum platinum is measurable years after therapy, its impact on NTX has not been evaluated.

Patients and Methods
In all, 169 cisplatin-treated survivors of TC provided blood samples at Survey I and reported NTX during Survey I (1998-2002) and Survey II (2007-2008). Serum platinum was quantified by inductively coupled plasma mass spectrometry. Patient-reported outcomes were evaluated with the Scale for Chemotherapy-Induced Neurotoxicity (SCIN), regarding the extent of symptom bother as 0, "not at all"; 1, "a little"; 2, "quite a bit"; or 3, "very much." Summing the six symptom scores yielded a total SCIN score of 0 to 18. Categorizing total SCIN scores into quartiles yielded similar-sized groups with increasing symptoms. Multivariate ordinal logistic regression analyses evaluated associations between NTX and long-term serum platinum levels, adjusting for cisplatin dose, dosing schedule, and age.

Results
At Survey I, a significant four- to five-fold association with total SCIN score emerged for the highest serum platinum quartile (odds ratio [OR], 4.69; 95% CI, 1.82 to 12.08). Paresthesias and Raynaud's syndrome (hands and feet) showed significant two- to four-fold increased risks with the highest platinum quartile. At Survey II, total SCIN score remained significantly associated with the highest platinum quartile (OR, 4.28; 95% CI, 1.36 to 13.48). Paresthesias (hands and feet) and tinnitus showed significant three- to four-fold increased risks for the highest platinum quartile. Cumulative cisplatin dose was not associated with total SCIN score or individual SCIN symptoms in multivariate analyses.

Conclusion
Here we document a significant relationship between increasing levels of residual serum platinum and NTX severity after adjusting for initial cisplatin dose.

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INTRODUCTION

Testicular cancer (TC) serves as a model for a curable neoplasm with 5-year survival rates exceeding 97%.[1,2] The improved prognosis is primarily due to cisplatin-based chemotherapy, the cornerstone of metastatic TC treatment.[3,4] Moreover, platinating agents comprise some of the most widely used cytotoxic drugs worldwide.

There is, however, increasing awareness about long-term toxicities following cisplatin-based chemotherapy, including potentially fatal events, such as cardiovascular disease (CVD), pulmonary dysfunction, and secondary neoplasms, years after treatment discontinuation.[5-14] Peripheral paresthesias, Raynaud's phenomenon, hearing impairment, and tinnitus represent platinum-induced toxicities,[15-19] with a prevalence of 30% to 40% in TC survivors (TCSs).[17,19,20] Both cumulative dose and administration schedule have an impact on development and severity of cisplatin-related neurotoxicity.[15] Functional polymorphisms in cisplatin-detoxifying enzymes, such as glutathione *S*-transferase, are also related to the severity of neurotoxicity.[21,22] Reasons for the large interindividual variation in long-term complications remain largely obscure. In the absence of effective remedies for these sequelae, identifying contributing factors for risk prediction and prevention is important.[11]

Total serum platinum level may represent a biomarker of late toxicity and body burden, since it can be measured years after application, with

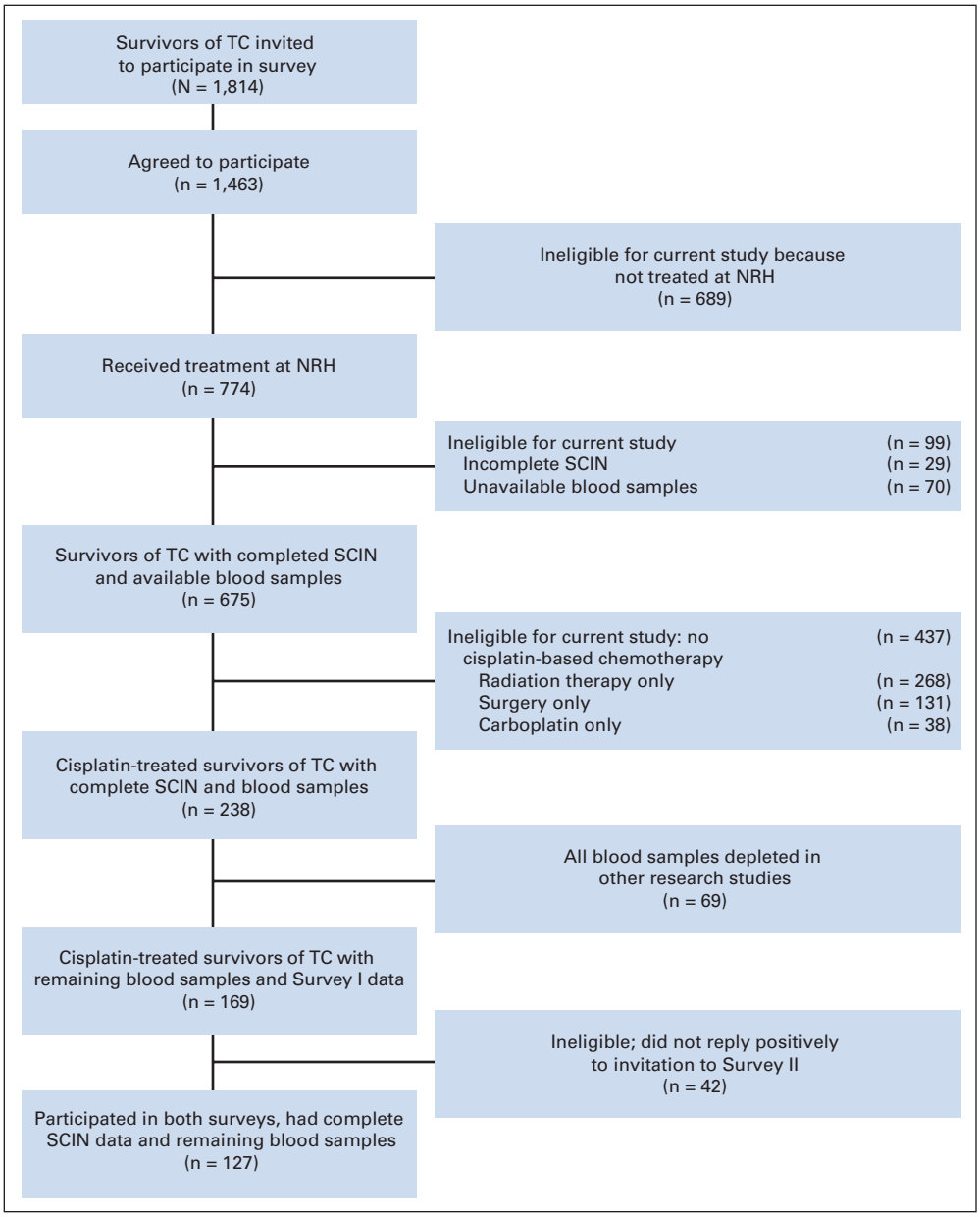

Fig 1. Overview of survivors of testicular cancer (TC) included in Survey I (2000), Survey II (2007), and this study (see Patients and Methods). NRH, Norwegian Radium Hospital; SCIN, Scale for Chemotherapy-Induced Neuropathy.

concentrations up to 1,000 times higher in cisplatin-treated patients than in unexposed controls.[23-26] Moreover, up to 10% of circulating platinum remains reactive.[23] Whether long-term total serum platinum is associated with development and severity of various cisplatin-related toxicities has not been assessed and was recommended a priority research item during an expert consensus conference.[11]

Our aim was to examine the association between long-term total serum platinum and the prevalence or severity of peripheral paresthesias, Raynaud's phenomenon, and ototoxicity in a well-characterized cohort of TCSs, taking into account cumulative cisplatin dose, time since treatment, and other variables. We hypothesized that residual long-term serum platinum levels would be positively associated with these sequelae, even when adjusted for initially administered cumulative cisplatin dose.

PATIENTS AND METHODS

Study Population and Design

From January 1998 through April 2002, a national follow-up survey (Survey I) was performed at all five Norwegian University hospitals to assess physical and psychosocial morbidity in long-term TCSs. All men treated for unilateral germ cell TC from January 1980 through December 1994 at age 18 to 75 years were identified through the Cancer Registry of Norway and regional university hospitals and were invited to participate (n = 1,814; Fig 1). A total of 81% of eligible men consented, completed a 219-item questionnaire, and underwent clinical examination at outpatient clinics. At the Norwegian Radium Hospital (NRH) only, blood samples were drawn during Survey I and stored at −70°C. Therefore, this study is restricted to TCSs treated at NRH. Blood samples had also been used in prior research projects,[21,22,27] but sufficient material remained for 169 previously cisplatin-exposed TCSs.

Questionnaire-based Survey II (2007) was performed a median 8 years (range, 7 to 9 years) after Survey I. Of 169 TCSs with blood samples in Survey I, 127 (75.1%) participated in Survey II. Both surveys were approved by the Norwegian Committee for Medical Research Ethics of the Southern Health Region.

Standards of Treatment, 1980 to 1994

Orchiectomy was typically the first step of treatment, with staging according to the Royal Marsden Hospital System.[28] From 1980 to 1994, most TCSs included in this study were treated according to protocols of the European Organisation for Research and Treatment for Cancer, the Medical Research Council, or the Swedish-Norwegian Testicular Cancer Project.[29-32]

Typically cisplatin was combined with bleomycin and either etoposide (BEP) or vinblastine (CVB). Thirty-one TCSs were randomly assigned to dose-intensive regimens in which cisplatin was applied over 2 or 3 days instead of 5 days or particularly high cumulative doses were given (Appendix, online only). Two patients received carboplatin-based chemotherapy and cisplatin-based regimens. The therapeutic dose of the two drugs has generally been described as a ratio of 4:1, based on clinical studies in ovarian cancer in which these doses achieved a relative equivalency.[33-35] On the basis of these results and procedures in a prior report by Travis et al,[36] we chose to calculate corresponding cisplatin doses by dividing carboplatin by four. The remaining patients received other types of cisplatin-based regimens.[29,31,37] Bleomycin was administered to 160 (94.7%) of 169 patients (median cumulative dose: 300,000 IU; range, 90,000 to 390,000 IU) and exceeded a total dose of 300,000 IU for only 32 patients, because most protocols specified 300,000 IU as the dose limit.[38] All patients received rigorous hydration regimens.

Questionnaire

A 219-item questionnaire[39] that included the validated six-item Scale for Chemotherapy-Induced Neurotoxicity (SCIN) was used in Survey I.[40] SCIN assessed neuropathy in hands (fingers) and feet (toes), Raynaud's phenomenon in hands (fingers) and feet (toes), tinnitus, and impaired hearing. For simplicity, we subsequently use the terms hands and feet. Item scores ranged from 0, "not at all"; 1, "a little"; and 2, "quite a bit;" to 3, "very much" (Appendix Table A1, online only). Summation of the six item scores yields a total score with a range of 0 to 18. Categorization of the total SCIN score into quartiles yielded four groups of similar size.

Survey II[27] consisted of an 83-item questionnaire including SCIN and also addressed tobacco use, comorbidities, medication use, and alcohol use (only Survey I).[15] Numbers with regard to alcohol abuse and diabetes were considered too small for statistical analyses.

Quantification of Serum Platinum Levels

In 2009, by using well-established methods,[41-43] serum samples from 169 TCSs were analyzed for total platinum blinded to the demographics or treatment of TCSs at the University of Massachusetts in Boston. The deep-frozen samples were shipped on dry ice, equilibrated at room temperature for 4 hours, and homogenized with a GlobalSpec laboratory slow shaker (GlobalSpec, East Greenbush, NY) for 30 minutes. Approximately 0.1 mL of serum was pipetted into a trace-metal-clean test tube and verified gravimetrically to $\pm$ 0.001 g. Samples were diluted by using 18.2 MΩ/cm^{-1} resistance water and acidified by using ultra-pure (12.4 mol/L^{-1}) hydrochloric acid. Known concentrations of indium, bismuth, and iridium were added to the samples and were used to monitor instrument drift.[42,43] Serum platinum concentrations were quantified by using a Perkin-Elmer DRC II inductively coupled plasma mass spectrometer (Perkin-Elmer, Norwalk, CT) by using external calibration procedures previously developed for other biologic tissues.[41-43a] Platinum detection was performed according to Brouwers et al.[43,44] Limits of platinum detection (0.010 pmol/g), quantification (0.035 pmol/g), and method detection (0.097 pmol/g) were calculated according to Long and Winefordner.[45]

Statistical Methods

Continuous variables were described with median and range, and categorical variables were described with counts and proportions. Crude associations between pairs of continuous variables were assessed by using Pearson correlation. The χ^2 test of trend was used to assess crude associations between pairs of ordered categorical variables. Associations between the SCIN scores and continuous variables were analyzed with ordinal logistic regression (OLR).

OLR was used to model total SCIN score and ordered individual SCIN symptoms as a function of administered cisplatin dose, dose-intensive versus standard chemotherapy, age at survey, and quartiles of serum platinum levels. Variables of high clinical relevance or those reaching $P < .2$ were included in OLR. Odds ratios (ORs) for any dichotomization of the four ordered outcome levels were reported for each independent predictor, along with 95% CIs. Adjusted tests of trend for serum platinum quartiles were based on refitting OLR models with serum platinum quartiles coded as 1, 2, 3, or 4 and modeled linearly in logit. A test of parallel lines checked the proportional odds assumption that the OR for each predictor was similar for all three possible dichotomizations of the outcome. ORs represent a comparison of higher to lower grouped ordered outcomes (ie, symptoms of "a little" or more *v* "not at all"; "very much" or "quite a bit" *v* "a little" or "not at all"; and "very much" *v* "quite a bit" or less). For tinnitus and hearing impairment, the two highest toxicity groups were pooled to remedy violations of this assumption; however, results were nearly identical without pooling. All tests were two-sided and were conducted at the 0.05 level of significance. Statistical analyses were performed by using SPSS 17.0 (SPSS, Chicago, IL).

RESULTS

Median age at TC diagnosis and at Survey I (n = 169 patients) was 28.7 years and 40.8 years, respectively (Table 1). Most TCSs presented with nonseminomatous tumors (81.1%) and metastatic disease (82.8%). Primary chemotherapy consisted of CVB (40.8%) and standard BEP (39.1%). Median cumulative dose of cisplatin was 401 mg/m^2 (range, 191 to 1,565 mg/m^2). Median serum platinum concentration was 0.769 nmol/L (range, 0.031 to 12.710 nmol/L) at a median of 12 years after treatment. Serum platinum was positively correlated with cumulative cisplatin dose (Pearson correlation, $P < .001$) and inversely correlated with time since treatment (Pearson correlation, $P < .001$). Serum platinum was significantly higher after administration of dose-intensive chemotherapy compared with standard chemotherapy (χ^2 trend, $P < .001$).

Since 127 (75.1%) of the 169 TCSs from Survey I also participated in Survey II, longitudinal neurotoxicity data were available for the majority of patients at a median of 20.0 years (range, 13.0 to 27.0 years) since the end of cisplatin-based treatment. Distribution of histology, stage, and cisplatin-based protocol for the 127 TCSs who participated in Survey II did not differ from that for the 169 participants in Survey I (Table 1).

Serum Platinum and Neurotoxicities in Survey I

Univariate analyses. Increasing serum platinum quartiles were significantly associated with increasing total SCIN score (Fig 2; χ^2 trend, $P < .001$) and Raynaud's phenomenon in hands and feet (χ^2 trend, $P = .004$ and $P = .001$, respectively; data not shown). Serum platinum levels were significantly higher after administration of dose-intensive chemotherapy compared with standard chemotherapy (χ^2 trend, $P < .001$). Ototoxicity (ie, tinnitus and hearing impairment) was also increased at Survey I for the dose-intensive group (χ^2 trend, $P = .002$ and $P = .001$, respectively). There were no statistical differences in symptom severity between men who received the CVB or the BEP regimen as their initial treatment (data not shown). Total SCIN score was positively associated with administered

Table 1. Demographics, Type of Cisplatin-Based Chemotherapy Regimen, and Lifestyle Factors for Cisplatin-Treated Survivors of TC* Participating in Surveys I and II

Characteristic	Survey I (2000) No.	Survey I (2000) %	Survey II (2007) No.	Survey II (2007) %
No. of patients	169		127/169	
Age at TC diagnosis, years				
Median	28.7		29.1	
Range	14.8-58.5		14.8-58.5	
Histology				
Seminoma	32	18.9	24	18.9
Nonseminoma	137	81.1	103	81.1
Age at survey, years				
Median	40.8		50.5	
Range	23.0-73.0		33.0-81.0	
Time between TC diagnosis and survey, years				
Median	12.0		20.0	
Range	4.0-19.0		13.0-27.0	
Royal Marsden stage				
I	29	17.2	21	16.5
IM	5	3.0	5	3.9
II	79	46.7	57	44.9
III	10	5.9	7	5.5
IV	46	27.2	37	29.1
Cisplatin-based regimens†				
Standard-dose regimens				
BEP 20	66	39.1	50	39.4
CVB	69	40.8	52	40.9
Others	3	1.8	2	1.6
Dose-intensive regimens				
BOP/VIP	9	5.3	8	6.3
BEP 40, 50, and 60	13	7.7	8	6.3
Others	9	5.3	7	5.5
Smoking status at survey‡				
Yes (current/former)	70	41.4	70	55.1
No (never/rare)	93	55.0	56	44.1
Missing	6	3.6	1	0.8

NOTE. Number of schedules could vary according to randomization in protocols, primary disease stage, and response during chemotherapy. Dose-intensive regimens are described in Appendix Table A1 (online only).

Abbreviations: BEP, cisplatin, etoposide and bleomycin; BOP, cisplatin, vincristine, and bleomycin; CVB, cisplatin, vinblastine, and bleomycin; TC, testicular cancer; VIP, cisplatin, etoposide, and ifosfamide.

*All 169 men initially underwent orchiectomy for TC, with staging uniformly performed according to the Royal Marsden Hospital Staging System.

†Standard cisplatin-based regimens. BEP 20: cisplatin 20 mg/m^2 days 1 through 5, etoposide 100 mg/m^2 on days 1 through 5, and bleomycin 30,000 IU on days 2, 5, and 15. CVB: cisplatin 20 mg/m^2 on days 1 through 5, vinblastine 6 mg/m^2 on days 1 and 2, and bleomycin 30,000 IU on days 2, 5, and 15. CEB: carboplatin at a formula of (5 × glomerular filtration rate + 125) on day 1, etoposide 120 mg/m^2 on days 1 through 3, and bleomycin at 30,000 IU on days 1, 8, and 15. EP: cisplatin 20 mg/m^2 on days 1 through 5, etoposide 100 mg/m^2 on days 1 through 5. HOP: cisplatin 20 mg/m^2 on days 1 through 5, ifosfamide 1,200 mg/m^2 on days 1 through 5, and vincristine 2 mg on day 1.

‡Smoking: current and former "regular smokers" were registered as smokers (ie, "yes"). Never smokers or those who "only smoked a few times" (ie, rarely) were grouped into the "no" category.

cisplatin dose, dose-intensive therapy, and age at survey (χ^2 trend, P = .016, P = .032, and P = .035, respectively). These variables were included in multivariate analyses for both surveys.

Multivariate analyses. Cumulative dose of cisplatin was not associated with either total SCIN score (OR, 1.10; 95% CI, 0.88 to 1.39)

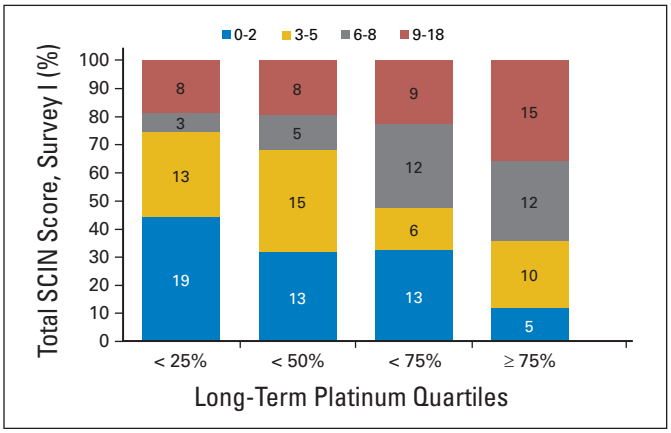

Fig 2. Number of survivors of testicular cancer according to quartile of serum platinum level and total Scale for Chemotherapy-Induced Neuropathy (SCIN) score at Survey I (2000).

or any of the individual symptoms (Table 2). In contrast, the highest compared with the lowest serum platinum quartile was significantly associated with total SCIN score (OR, 4.69; 95% CI, 1.82 to 12.08). Furthermore, risk of experiencing individual symptoms was increased two- to four-fold for TCSs in the highest compared with the lowest platinum quartile for paresthesias in hands (OR, 2.87; 95% CI, 1.08 to 7.62) and feet (OR, 2.83; 95% CI, 1.09 to 7.40) and Raynaud's phenomenon in hands (OR, 4.15; 95% CI, 1.60 to 10.76) and feet (OR, 4.46; 95% CI, 1.70 to 11.71).

Age had a significant impact on total SCIN score (OR, 1.71; 95% CI, 1.25 to 2.32), paresthesias in hands (OR, 1.44; 95% CI, 1.06 to 1.96) and feet (OR, 1.86; 95% CI, 1.36 to 2.54), tinnitus (OR, 1.44; 95% CI, 1.05 to 1.98), and hearing impairment (OR, 1.89; 95% CI, 1.35 to 2.64). Dose-intensive therapy had a significant impact on tinnitus and hearing impairment (OR, 2.63; 95% CI, 1.08 to 6.25 and OR, 4.00; 95% CI, 1.61 to 10.00, respectively).

Survey II

Univariate analyses. Increasing serum platinum quartiles were significantly associated with total SCIN score (Fig 3; χ^2 trend, P = .007). Serum platinum quartiles were significantly associated with five of six self-reported SCIN symptoms; paresthesias in hands and feet, Raynaud's phenomenon in the feet, tinnitus, and impaired hearing (χ^2 trend, P values between .003 and .033; data not shown). Hearing impairment was significantly associated with dose-intensive therapy (χ^2 trend, P = .002), whereas a borderline significant relationship existed for tinnitus (χ^2 trend, P = .094). Cisplatin dose, dose-intensive therapy, and age did not reach significance for total SCIN score, but significant differences emerged for some SCIN symptoms.

Multivariate analyses. Cumulative dose of cisplatin was not significantly associated with either total SCIN score (OR, 1.01; 95% CI, 0.78 to 1.30) or with any of the individual symptoms (Table 3). Similar to Survey I, a significant four-fold increased association with total SCIN score (OR, 4.28; 95% CI, 1.36 to 13.48) was found for the highest compared with the lowest serum platinum quartile. The highest quartile of serum platinum was also associated with significantly increased four- to five-fold risks of paresthesias in hands (OR, 4.08; 95% CI, 1.29 to 12.93) and feet (OR, 4.63; 95% CI, 1.45 to 14.76). Similarly, increased three-fold risks were observed for Raynaud's phenomenon in

Table 2. Adjusted Associations of SCIN Symptoms at Survey I With Serum Platinum Quartiles, Administered Cisplatin Dose, Dose-Intensive Therapy, and Age[a]

	Survey I (2000)												
	Administered Cisplatin Dose[b]		Dose-Intensive Therapy (yes/no)[c]		Age at Survey[d]		Quartile of Serum Platinum Level[e]						
Symptom	OR	95% CI	OR	95% CI	OR	95% CI	25 to 50 OR	95% CI	50 to 75 OR	95% CI	> 75 OR	95% CI	Adjusted *P* for Trend[f]
Total score	1.10	0.88 to 1.39	1.35	0.57 to 3.23	1.71[c]	1.25 to 2.32	1.26	0.57 to 2.80	1.79	0.79 to 4.04	4.69[g]	1.82 to 12.08	.002[g]
Paresthesias hands	0.90	0.71 to 1.15	1.12	0.46 to 2.78	1.44[g]	1.06 to 1.96	1.08	0.36 to 2.18	1.31	0.55 to 3.13	2.87[g]	1.08 to 7.62	.044[g]
Paresthesias feet	1.15	0.92 to 1.45	0.75	0.31 to 1.82	1.86[g]	1.36 to 2.54	1.15	0.50 to 2.65	1.27	0.54 to 2.97	2.83[g]	1.09 to 7.40	.055
Raynaud's phenomenon hands	0.94	0.75 to 1.17	1.22	0.51 to 2.86	1.26	0.94 to 1.71	1.07	0.46 to 2.46	1.56	0.67 to 3.60	4.15[g]	1.60 to 10.76	.003[g]
Raynaud's phenomenon feet	1.10	0.88 to 1.38	0.74	0.31 to 1.79	1.31	0.97 to 1.78	1.18	0.50 to 2.77	1.83	0.78 to 4.31	4.46[g]	1.70 to 11.71	.002[g]
Tinnitus[h]	1.14	0.89 to 1.44	2.63[g]	1.08 to 6.25	1.44[g]	1.05 to 1.98	1.38	0.58 to 3.32	1.22	0.50 to 3.02	1.56	0.57 to 4.26	.457
Hearing impairment[h]	1.16	0.90 to 1.48	4.00[g]	1.61 to 10.00	1.89[g]	1.35 to 2.64	1.46	0.60 to 3.57	1.99	0.81 to 4.93	1.80	0.64 to 5.07	.174

Abbreviations: OR, odds ratio; SCIN, Scale for Chemotherapy-Induced Neurotoxicity.
[a]Associations were assessed with multivariable ordinal logistic regression analyses and are presented with ORs and 95% CIs. ORs represent a comparison of higher with lower grouped and ordered patient outcomes (ie, symptoms of "a little" or more *v* "not at all"; "very much" or "quite a bit" *v* "a little" or "not at all"; and "very much" *v* "quite a bit" or less, assuming all three dichotomizations have the same OR) per decade of age, per 100 mg/m^2 increase of administered cisplatin, and for each quartile of serum platinum compared with the lowest quartile (referent group).
[b]Administered cisplatin per 100 mg/m^2. This category includes both standard-dose and dose-intensive regimens.
[c]A yes/no indicator of dose-intensive *v* standard chemotherapy.
[d]Increase in indicated symptom per decade of patient age.
[e]Serum platinum was quantified in blood samples obtained at Survey I (2000).
[f]Adjusted *P* value for trend testing the effect of serum platinum level modeled as a continuous function of quartile score (1, 2, 3, 4) in the ordinal logistic regression model, adjusted for age, administered cisplatin dose, and dose-intensive therapy.
[g]$P < .05$ (two-sided) was considered statistically significant.
[h]For analyses of tinnitus and hearing impairment, the top two toxicity groups were pooled in each survey.

hands (OR, 3.11; 95% CI, 0.97 to 9.94) and feet (OR, 2.80; 95% CI, 0.90 to 8.71) and tinnitus (OR, 3.44; 95% CI, 1.03 to 11.54). Age had an impact on the total SCIN score, with an OR per decade of 1.43 (95% CI, 1.03 to 1.99). Further, paresthesias in the feet (OR, 1.66; 95% CI, 1.19 to 2.33) and hearing impairment were significantly associated with increasing age (OR, 1.86; 95% CI, 1.29 to 2.68). We found no significant impact of dose-intensive therapy on tinnitus and hearing impairment at Survey II.

DISCUSSION

To the best of our knowledge, this is the first study demonstrating that long-term serum platinum levels are significantly associated with the severity of neurotoxicity 5 to 20 years after cisplatin-based chemotherapy. Importantly, the relationship remained significant after adjustment for initial cisplatin dose. Serum platinum quartiles were positively associated with overall neurotoxicity and ototoxicity as assessed by total SCIN scores at Surveys I and II (*P* trend = .002 and .032, respectively), as were most individual symptoms.

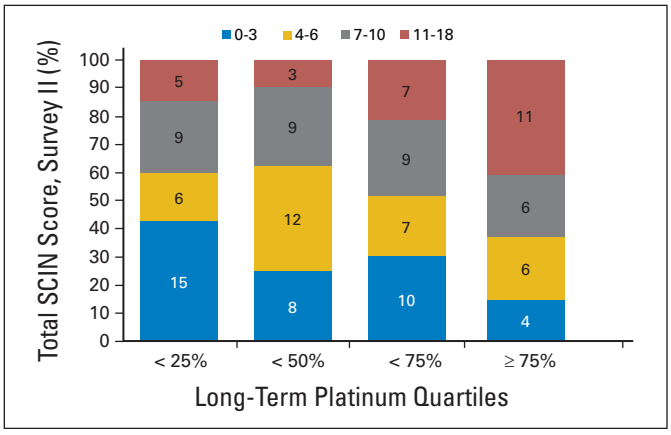

Fig 3. Number of survivors of testicular cancer according to quartile of serum platinum level and total Scale for Chemotherapy-Induced Neuropathy (SCIN) score at Survey II (2007).

Strengths of our study include a large well-characterized cohort of TCSs with long-term follow-up and detailed information regarding cancer therapy. All men were treated at the same hospital and underwent standardized examinations at Surveys I and II. The high participation rate ensures validity of our findings.

Although our study is derived from the largest cohort of TCSs to date,[5,10,15,22,27] numbers of patients available in various subgroup analyses remain small, limiting statistical power. Serum platinum levels were available for Survey I only, precluding calculation of platinum elimination rates. The questionnaires, however, were collected at both Survey I and Survey II. Interpretation of our findings would have been stronger if the symptom measurements and serum platinum levels had been measured in a longitudinal fashion at both surveys, also including objective measurements.

Reliance on self-reported symptoms without objective measurements is a limitation of this study. Ototoxicity as recorded on the SCIN was previously validated among these patients through objective measurements.[39] Neurologic tests, however, were not performed in our study. Other studies observed that, compared with self-report, prevalence of adverse effects may be higher when measured objectively.[39,46]

Most patients received cisplatin in combination with bleomycin, usually regarded as the principal cause of Raynaud's phenomenon. However, cisplatin might also contribute to cold-induced vasospasms. Vogelzang et al[47] reported the incidence of Raynaud's phenomenon to

Table 3. Adjusted Associations of SCIN Symptoms at Survey II With Serum Platinum Quartiles, Administered Cisplatin Dose, Dose-Intensive Therapy, and Age[a]

	Survey II (2007)												
	Administered Cisplatin Dose[b]		Dose-Intensive Therapy (yes/no)[c]		Age at Survey[d]		Quartile of Serum Platinum Level[e]						
Symptom	OR	95% CI	OR	95% CI	OR	95% CI	25 to 50 OR	95% CI	50 to 75 OR	95% CI	> 75 OR	95% CI	Adjusted *P* for Trend[f]
Total score	1.01	0.78 to 1.30	1.22	0.43 to 3.57	1.43[g]	1.03 to 1.99	1.22	0.51 to 2.93	1.45	0.59 to 3.59	4.28[g]	1.36 to 13.48	.032[g]
Paresthesias hands	0.96	0.74 to 1.24	1.12	0.39 to 3.23	1.25	0.90 to 1.74	2.22	0.90 to 5.47	1.60	0.63 to 4.04	4.08[g]	1.29 to 12.93	.043[g]
Paresthesias feet	1.14	0.88 to 1.48	0.67	0.23 to 1.92	1.66[g]	1.19 to 2.33	1.44	0.59 to 3.53	2.05	0.81 to 5.16	4.63[g]	1.45 to 14.76	.013[g]
Raynaud's phenomenon hands	0.89	0.67 to 1.17	0.63	0.22 to 1.85	0.97	0.70 to 1.35	0.91	0.38 to 2.19	1.04	0.42 to 2.59	3.11	0.97 to 9.94	.120
Raynaud's phenomenon feet	1.04	0.81 to 1.34	0.77	0.27 to 2.22	1.14	0.82 to 1.59	0.79	0.32 to 1.95	1.54	0.62 to 3.84	2.80	0.90 to 8.71	.072
Tinnitus[h]	0.98	0.75 to 1.28	1.43	0.47 to 4.35	1.18	0.84 to 1.66	2.54	1.00 to 6.52[g]	2.05	0.78 to 5.43	3.44[b]	1.03 to 11.54	.055
Hearing impairment[h]	1.32	0.94 to 1.85	2.94	0.92 to 9.09	1.86[g]	1.29 to 2.68	0.86	0.35 to 2.16	1.04	0.40 to 2.70	1.33	0.39 to 4.55	.688

Abbreviations: OR, odds ratio; SCIN, Scale for Chemotherapy-Induced Neurotoxicity.

[a]Associations were assessed with multivariable ordinal logistic regression analyses and are presented with ORs and 95% CIs. ORs represent a comparison of higher with lower grouped and ordered patient outcomes (ie, symptoms of "a little" or more *v* "not at all"; "very much" or "quite a bit" *v* "a little" or "not at all"; and "very much" *v* "quite a bit" or less, assuming all three dichotomizations have the same OR) per decade of age, per 100 mg/m^2 increase of administered cisplatin, and for each quartile of serum platinum compared with the lowest quartile (referent group).

[b]Administered cisplatin per 100 mg/m^2. This category includes both standard-dose and dose-intensive regimens.

[c]A yes/no indicator of dose-intensive *v* standard chemotherapy.

[d]Increase in indicated symptom per decade of patient age.

[e]Serum platinum was quantified in blood samples obtained at Survey I (2000).

[f]Adjusted *P* value for trend testing the effect of serum platinum level modeled as a continuous function of quartile score (1, 2, 3, 4) in the ordinal logistic regression model, adjusted for age, administered cisplatin dose, and dose-intensive therapy.

[g]$P < .05$ (two-sided) was considered statistically significant.

[h]For analyses of tinnitus and hearing impairment, the top two toxicity groups were pooled in each survey.

be 21% after vinblastine and bleomycin compared with 41% after therapy with CVB. In the comprehensive report by Brydoy et al,[15] Raynaud's phenomenon was not associated with bleomycin in contrast to a dose-dependent effect observed for cisplatin and dose-intensive cisplatin-based chemotherapy.

Studies performed within 15 months after cisplatin administration,[48-51] show increased platinum levels in most organs. In human autopsies conducted 4 to 867 days after the last cisplatin dose, platinum concentrations were highest in dorsal root ganglia and lowest in tissues protected by the blood-brain barrier, in line with observations of sensory neuropathies and histopathologically documented peripheral nerve damage.[48] Subsequent rates of decline in tissue platinum are lowest in sensory ganglia, sural nerves, and liver.[48] Previous data have suggested that both the incidence and severity of neurotoxicity are mainly determined by the cumulative cisplatin dose, and are determined for ototoxicity also by the dose-intensive regimen.[15,52,53] However, in our study, the highest long-term serum platinum levels were most strongly correlated with the severity of SCIN, even when adjusted for initial cisplatin dose. A possible explanation for this finding is that ongoing exposure to low-level platinum in neural tissue, as well as any residual systemic effects, may limit resolution of the acute and dose-dependent sensory neuropathy, hypothetically also contributing to ongoing damage.[54]

The biokinetic behavior of platinum closely resembles that of other toxic metals (eg, mercury and chromium[55,56]) in which serum and urine concentrations also correlate with toxic outcomes.[55,57] Importantly, Brouwers et al[23] showed that approximately 10% of platinum remains reactive over the long term.

Similar to prior studies,[23,24,26] we found a significant relationship between initial dose and platinum levels and an inverse relationship between time since administration and platinum levels. Future efforts evaluating the potential toxic impact of circulating serum platinum would benefit from the prospective collection of larger sample volumes, because available amounts did not permit determination of reactive platinum hypothesized by some to be the pharmacologically and toxicologically active species.[23]

Several studies of TCSs have demonstrated ongoing endothelial changes for more than 10 years after cisplatin administration, indicating a possible prolonged effect of residual platinum.[6,54,58] In particular, Vaughn et al,[54] showed endothelial damage in TCSs at a median of 5.1 years after cisplatin-based treatment. These investigators postulated that the increased risk of CVD in TCSs could be due partly to persistent exposure of endothelial cells to circulating platinum. Other studies have shown an increased risk for late CVD in TCSs given cisplatin-based chemotherapy.[6,10,12,59] It may also contribute to increased risk of metabolic syndrome in TCSs;[5,6] however, results are inconclusive.[10]

Several studies[8,12,13,60] have shown significantly increased risks of solid tumors and leukemia[9] among cisplatin-treated TCSs. Whether cisplatin in tissue deposits or in circulating form, alone or with other agents, may serve an initiating or promoting carcinogenic role is not known.

Our results suggest that interventional strategies reducing long-term platinum levels may show promise for lessening long-term neurotoxicity, with the importance of further studies in this area recently underscored by a National Cancer Institute panel.[61] Currently, to the best of our knowledge, there are no agents that ameliorate the clinical neurotoxicity of platinating agents. According to a recent Cochrane Database review,[62] information on possible neuroprotective agents, such as acetylcysteine, amifostine, calcium and magnesium, diethyldithiocarbamate, glutathione, Org 2766, oxycarbazepine,or vitamin E

are insufficient to conclude that they "prevented or limited neurotoxicity of platinum drugs among human patients."

Importantly, we do not question the use of cisplatin in the treatment of metastatic TC, because this drug is still the cornerstone of the chemotherapy that rendered this cancer a model for a curable neoplasm.[3,4] Whether carboplatin would have less long-term toxicity is unknown; however, carboplatin would decrease the cure rate.[63] Nonetheless, we demonstrate that long-term serum levels of platinum correlate with the severity of neurotoxicity 5 to 20 years after chemotherapy in TCSs. Although chemotherapy-induced neuropathies are not life threatening, symptoms can have a debilitating effect on patients' quality of life and functioning. Increasing knowledge about the long-term effects of circulating platinum underscores the importance of interventional strategies to minimize platinum-related neurotoxicity and ototoxicity and potentially fatal events such as myocardial infarction and secondary malignancies. To validate our findings and to elucidate the underlying mechanisms of toxicities related to the effect of reactive platinum, we emphasize the importance of further studies on the impact of residual platinum in an independent large cohort of platinum-treated survivors of cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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